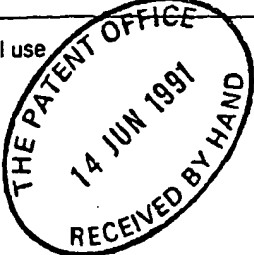


14 JUN 1991

	18 JUN 91 H00282438 PAT 1 77 UC 15.00
Your reference PH. 36403/21/P	9112825.6

Notes

Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-829 6910).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

Warning

After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

The Patent Office
Request for grant of a Patent
Form 1/77
Patents Act 1977

1 Title of invention

1 Please give the title of the invention
 PROCESS FOR MAKING PEPTIDES

2 Applicant's details☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name IMPERIAL CHEMICAL INDUSTRIES PLC

Country (and State of incorporation, if appropriate) United Kingdom

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c In all cases, please give the following details:

Address Imperial Chemical House,
 Millbank,
 London.

UK postcode SW1P 3JF
 (if applicable)

Country United Kingdom
 ADP number 935003
 (if known) ✓

2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant (if any)**

2d If you are applying as a corporate body please give:

Corporate name

Country (and State
of incorporation, if
appropriate)

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f In all cases, please give the following details:

Address

UK postcode
(if applicable)

Country

ADP number
(if known)

Ⓢ An address for service in the
United Kingdom must be supplied

Please mark correct box

Ⓢ Address for service details

3a Have you appointed an agent to deal with your application?

Yes ☒ No ☐ → go to 3b

↓
please give details below

Agent's name Reginald Peter Slatcher

Agent's address Legal Department: Patents
Imperial Chemical Industries PLC
P O Box 6, Bessemer Road
Welwyn Garden City
Hertfordshire

Postcode AL7 1HD

Agent's ADP
number 01320837001

01320837002 *AL*

3b: If you have appointed an agent, all
correspondence concerning your
application will be sent to the agent's
United Kingdom address.

3b If you have not appointed an agent please give a name and address in the
United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

ADP number
(if known)

Daytime telephone
number (if available)

① Reference number

4 Agent's or
applicant's reference
number (if applicable)

AI-36402/AA/P

⑥ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐

No ☒ → go to 6

↓
please give details below

☐ number of earlier
application or patent
number

☐ filing date

(day month year)

☐ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

⑥ If you are declaring priority from a
PCT Application please enter 'PCT' as
the country and enter the country
code (for example, GB) as part of the
application number.

Please give the date in all number
format, for example, 31/05/90 for
31 May 1990.

⑥ Declaration of priority

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number (if known)	Filing date (day, month, year)

- 7 The answer must be 'No' if:
- any applicant is not an inventor
 - there is an inventor who is not an applicant, or
 - any applicant is a corporate body.

8 Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

- 9 You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

Please sign here →

A completed fee sheet should preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐ No ☒ → A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77

Claim(s)

Description

12

Abstract

Drawing(s)

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority documents (please state how many)

Patents Form 7/77 – Statement of Inventorship and Right to Grant
(please state how many)

Patents Form 9/77 – Preliminary Examination/Search

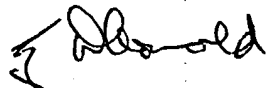
Patents Form 10/77 – Request for Substantive Examination

9 Request

I/We request the grant of a patent on the basis of this application.

IMPERIAL CHEMICAL INDUSTRIES PLC

Signed



Date 14 16 191.

day month year

AUTHORISED OFFICER

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

□ The Comptroller
The Patent Office
State House
66-71 High Holborn
London
WC1R 4TP

PROCESS FOR MAKING PEPTIDES

This invention relates to a process for making peptides and more particularly it relates to a solid phase peptide synthesis method for the preparation, inter alia, of the decapeptide goserelin.

The solid phase synthesis of peptides has been known for almost 30 years following the pioneering work of Merrifield first published in 1962. The general principle of this type of synthesis is as follows:-

- (a) An N-protected amino acid (the protecting group is commonly t-butoxycarbonyl, abbreviated to Boc) is attached to a solid, non-soluble support (commonly a polystyrene resin) at its carboxylic end via a linking group (commonly a benzyl ester).
- (b) The N-protecting group is removed by means which do not detach the amino acid from the solid support, and a second N-protected amino acid is coupled to the one already attached (commonly by use of a carbodi-imide coupling agent).
- (c) The sequence is repeated using as many N-protected amino acids as are required until the desired peptide has been formed, still attached at its carboxyl end to the solid support.
- (d) The final N-protecting group is removed and the peptide is separated from the solid support by cleavage of the linking group (commonly by use of a strong acid).

The whole synthesis can be machine-aided and in some circumstances the peptide may be formed without manual intervention. The Boc protecting groups are removed by trifluoroacetic acid and the peptide chain is removed from the solid support with a stronger acid such as hydrofluoric acid.

Since the introduction of this technique many modifications have been introduced, but the process is essentially as first proposed. Two major

innovations have been the use of a polyamide as the solid support and the use of a N-fluoren-9-ylmethoxycarbonyl (Fmoc) protecting group for the N- α -group of the amino acid. The Fmoc group is distinguished by being labile to base (commonly piperidine). For further detail reference is made, for example, to Atherton and Sheppard, "Solid phase peptide synthesis - a practical approach", IRL Press at Oxford University Press, 1989; Barany et al., "Solid-phase peptide synthesis: a silver anniversary report", Int. J. Peptide Protein Res., 1987, 30, 705-739 and Fields et al., *ibid*, 1990, 35, 161-214.

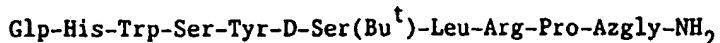
Throughout this specification standard abbreviations for amino acids, protecting groups, coupling agents and the like will be used. For the avoidance of doubt, as well as Boc and Fmoc defined above, the following are relevant standard abbreviations:-

Arg	arginine
Azala	aza-alanine ($H_2N-NMe-COOH$)
Azgly	azaglycine ($H_2N-NH-COOH$)
Azphe	azaphenylalanine ($H_2N-NBzl-COOH$)
D-Ser	D-serine
Glp	pyroglutamic acid
His	histidine
Leu	leucine
Pro	proline
Ser	serine
Trp	tryptophan
Tyr	tyrosine
DIPC	di-isopropylcarbodi-imide
HOBt	1-hydroxybenzotriazole
DIEA	di-isopropylethylamine
DMF	<u>N,N</u> -dimethylformamide
Bu ^t	tert-butyl
Bzl	benzyl
Su	succinimido

Goserelin is an LHRH analogue used in the treatment of prostate cancer, breast cancer and certain gynaecological conditions. In the

- 3 -

first-mentioned treatment it acts by inducing a chemical castration.
Its structure is:-



It will be seen that there are two features of this structure which are incompatible with traditional solid phase peptide synthetic routes. The first is the Azgly carboxy terminal amino acid; procedures for linking such a group to a solid support are not known. Free azaglycine has a terminal -NH-COOH group, which is an unstable carbamic acid.

The second is the t-butyl group attached to the D-serine moiety; in order to preserve this group traditional means for removing the completed peptide from the solid support cannot be used.

We have now found a method of preparing goserelin and similar peptides by solid phase synthesis.

According to the invention there is provided a method for solid phase synthesis of a peptide containing a C-terminal aza-amino acid, which comprises (i) reacting an (N-protected aza-aminoacyl) active ester with an appropriate reactive solid support;

(ii) carrying out a conventional solid phase peptide synthesis to form a peptide with the required number of amino acids bound to the support; and

(iii) cleaving the peptide from the support.

A suitable active ester which enables reaction with the solid support is, for example, a succinimido, benzotriazol-1-yl, pentafluorophenyl, 2,4,5-trichlorophenyl or 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl ester.

The reactive solid support may be a conventional one based on a cross-linked polystyrene resin into which chloromethyl groups have been introduced which in turn have been reacted with a phenoxy group. A particularly preferred support is one known as Fmoc-NH-Rink-resin.

Suitable C-terminal aza-amino acids are, for example, azaglycine, aza-alanine and azaphenylalanine.

The (N-protected-aza-aminoacyl) active esters used as starting materials are novel compounds, and these form a further feature of the invention. In particular, Fmoc-Azgly-OSu, Fmoc-Azala-OSu, Fmoc-Azphe-OSu, Fmoc-Azala-OBt and Fmoc-Azphe-OBt are specific features of the invention.

According to a further feature of the invention there is provided a method for solid phase synthesis of a peptide containing an amino acid which contains a t-butyloxy group in its sidechain, which comprises the use of a linking group connecting the C-terminal amino acid to the solid support which linking group is labile under conditions which do not cleave an O-t-butyl group.

A suitable linking group is that provided by Fmoc-NH-Rink-resin, namely the 4-(α -Fmoc-amino-2',4'-dimethoxybenzyl)phenoxy group which is attached to the methylene groups on the polystyrene resin. Peptides linked through this group may be cleaved from the support by short term treatment with low concentrations of an acid such as trifluoroacetic acid, which treatment will not cleave the t-butyl ether.

The amino acids contained in such a peptide are the t-butyl ethers of, for example, serine, D-serine, threonine, tyrosine and hydroxyproline.

According to a further feature of the invention there is provided a method for the solid phase synthesis of a peptide containing a C-terminal aza-amino acylamide, which comprises

- (i) reacting an (N-protected aza-aminoacyl) active ester with an appropriate reactive solid support;
- (ii) carrying out a conventional solid phase peptide synthesis without the use of protecting groups on the sidechains of the amino acids serine, arginine, tyrosine, threonine and hydroxyproline;
- (iii) cleaving the peptide from the solid support; and
- (iv) reacting the product so formed with hydrazine.

Suitable activated groups and solid supports are those defined above.

During the final stage of this process any acylated sidechain groups which have been formed are deacylated by the hydrazine.

The invention is illustrated but not limited by the following examples:-

Example 1

(a) Synthesis of
N¹-Fluoren-9-ylmethoxycarbonyl-N²-succinimido-oxycarbonylhydrazine
(Fmoc-Azgly-OSu)

A solution of 95% aqueous hydrazine (1.28ml) in acetonitrile (100ml) was added dropwise during 2 hours at laboratory temperature to a stirred solution of fluoren-9-ylmethyl succinimido carbonate (Fmoc-OSu, 13.48g) in acetonitrile (200ml) and the mixture was stirred for a further 16 hours and then filtered. The solid residue was washed with a 1:1 v/v mixture of acetonitrile and diethyl ether and then with diethyl ether, and then dried. There was thus obtained fluoren-9-ylmethoxycarbonylhydrazine (7.81g). A further 0.96g of this material was obtained by concentration of the filtrate and washings, filtration and crystallisation of the solid residue from ethanol.

The above hydrazide (8.77g) and disuccinimido carbonate (9.72g) were added at laboratory temperature to acetonitrile (150ml) and the mixture was stirred for 10 minutes until full solution was achieved, and then for a further 20 hours, and was then evaporated to dryness. A solution of the residue in ethyl acetate was washed successively with saturated aqueous sodium bicarbonate solution, water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness. The residue was stirred with petroleum ether (b.p. 60-80°C.), the mixture was filtered and the solid residue was dried. There was thus obtained Fmoc-Azgly-OSu (11.81g, 87% yield), the structure of which was confirmed by FAB mass spectroscopy, H¹-NMR at 250MHz and

elemental analysis.

(b) Attachment of Fmoc-Azgly-OSu to resin

All solid phase reactions were carried out at laboratory temperature using a Biosearch 9500 Peptide Synthesizer. All coupling reactions used 4 molar equivalents of acylating component.

4-(α -Fmoc-amino-2',4'-dimethoxybenzyl)phenoxy-polystyrene resin cross-linked with 1% divinylbenzene (Fmoc-NH-Rink-resin, 1g, 0.64meq/g) was treated with a 20% v/v solution of piperidine in DMF to remove the Fmoc group, washed with DMF and then reacted for 1 hour with 4 molar equivalents of Fmoc-Azgly-OSu as an 0.2 molar solution in DMF.

(c) Formation of decapeptide goserelin

The remaining 9 amino acids were sequentially added to the above resin using the Synthesizer in automatic mode. In all cases the coupling agent used was di-isopropylcarbodi-imide (DIPC), and the amino acids (apart from Glp used at the final stage which did not require protection) were protected at the amino end by Fmoc. Histidine (used at stage 8) was bis-protected by Fmoc; no protecting group was used for any other amino acid with a functional group in its sidechain. Reaction conditions varied slightly for each stage, as follows:-

(i) Addition of Pro

The following sequence of operations was performed:-

DMF wash

20% piperidine in DMF (2 minutes)

20% piperidine in DMF (8 minutes)

DMF wash

Fmoc-Pro-OH/DIPC/DMF

DMF wash

- 7 -

(ii) Addition of Arg

Although in automatic mode, the progress of the acylation was monitored by Kaiser analysis and extended when necessary. The following sequence of operations was performed:-

DMF wash

20% piperidine in DMF (2 minutes)

20% piperidine in DMF (8 minutes)

DMF wash

Fmoc-Arg(HCl)-OH/DIPC/DMF (2.5 hours)

DMF wash

10% DIEA/DMF wash (5 minutes)

DMF wash

0.5 molar HOBt/DMF wash (5 minutes)

Fmoc-Arg(HCl)-OH/DIPC/DMF (1.5 hours)

DMF wash

(iii) to (vii) inclusive - addition of Leu, D-Ser(Bu^t), Tyr, Ser, Trp

The following sequence of operations was performed:-

DMF wash

20% piperidine in DMF (2 minutes)

20% piperidine in DMF (8 minutes)

DMF wash

0.5 molar HOBt/DMF wash (5 minutes)

Fmoc-(amino acid)-OH (the amino acids in sequence)/DIPC/DMF (1 hour)

(viii) Addition of His

The sequence set out above for (iii) to (vii) was repeated except that the relatively insoluble Fmoc-His(Fmoc)-OH was added manually rather than automatically.

(ix) Addition of Glp

- 8 -

The sequence set out above for (iii) to (vii) was repeated. The resin was then washed with DMF and finally with methylene dichloride, and then dried.

(d) Cleavage of peptide from resin

The peptide resin prepared above (0.3g) was treated twice for 3 minutes each time at laboratory temperature with a solution of trifluoroacetic acid (200 μ l) in methylene chloride (10ml) and the mixture was filtered into a vessel containing triethylamine (800 μ l). The resin was washed with methylene chloride and then with methanol and the combined filtrate and washings were evaporated to dryness. The residue was dissolved in methanol and the solution was evaporated to dryness. The residue was dissolved in water (20ml), 95% aqueous hydrazine (100 μ l) was added and the mixture was kept at laboratory temperature for 2 hours. The mixture was filtered, acetonitrile (sufficient for it to be 5% by volume of the mixture) was added to the filtrate and the solution was loaded directly onto a reverse phase chromatography column (Dynamax, C₁₈, 300Å, 12 μ m, 25cm x 2.25cm). The column was eluted with a gradient (5% rising to 18% by volume) of acetonitrile in water containing 0.1% trifluoroacetic acid. The appropriate fractions were pooled and lyophilized and there was thus obtained goserelin (73mg), the structure of which was confirmed by amino acid analysis and mass spectroscopy.

Example 2

Synthesis of Fluoren-9-ylmethyloxycarbonyl-oxy-succinimide

Fmoc-OSu (16.86g) was added at laboratory temperature to a stirred solution of N¹-Boc-N¹-methylhydrazine (g) in acetonitrile (75ml) and the reaction mixture was heated under reflux for 4.5 hours and then kept at laboratory temperature for a further 72 hours. The reaction mixture was evaporated to dryness and the residue was partitioned between water and methylene chloride. The methylene chloride layer was separated, washed with saturated aqueous sodium chloride solution,

dried over sodium sulphate and evaporated to dryness. The residual gum was dissolved in chloroform (70ml) and the solution was loaded onto a column of silica gel (Merck Kieselgel 60/9385, 5x30cm) and eluted with chloroform followed by chloroform/methanol (99.5/0.5 v/v). The appropriate fractions were pooled and evaporated to dryness and there was thus obtained N¹-tert-butoxycarbonyl-N¹-methyl-N²-(fluoren-9-ylmethoxycarbonyl)hydrazide as a yellow gum (8.75g), the structure of which was confirmed by FAB mass spectroscopy (MH⁺ = 369).

A 5.2 molar solution of hydrogen chloride in ethyl acetate (10ml) was added at laboratory temperature to a stirred solution of the above product (4.6g) in ethyl acetate (15ml). After 25 minutes, a white precipitate had formed. The solid was collected by filtration, washed with diethylether and dried. There was thus obtained N¹-fluoren-9-ylmethoxycarbonyl-N²-methylhydrazine (N¹-Fmoc-N²-methylhydrazine) hydrochloride ((2.5g), the structure of which was confirmed by FAB mass spectroscopy (MH⁺ = 269).

Triethylamine (1.5ml) and bis-succinimido carbonate (BSC, 2.56g) were added successively to a stirred suspension of the above hydrazide hydrochloride (3.05g) in acetonitrile (30ml) at laboratory temperature. A further two 0.5g portions of BSC were added to the stirred reaction mixture after 15 and 30 minutes respectively. After 2 hours the reaction mixture was evaporated to dryness and the residue was heated with ethyl acetate (50ml) and saturated aqueous sodium bicarbonate. The ethyl acetate layer was separated, washed with saturated aqueous sodium bicarbonate solution and then with saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated to dryness. The residue was dissolved in chloroform and the solution was loaded onto a silica gel column (Merck Kieselgel 60/9385, 40x2cm) and eluted successively with chloroform, chloroform/methanol (99.5 : 0.5 v/v) and chloroform/methanol (99 : 1 v/v). The appropriate fractions were pooled and evaporated to dryness to give Fmoc-Azala-OSu as a white foam (2.8g).

Example 3Synthesis ofN¹-Fluoren-9-ylmethoxycarbonyl-N²-methyl-N²-succinimido-oxycarbonylhydrazine (Fmoc-Azphe-OSu)

A solution of N¹-tert-butoxycarbonyl-N¹-benzylhydrazine (8.84g) in acetonitrile (20ml) was added to a solution of Fmoc-OSu (13.43g) in acetonitrile (150ml) and the reaction mixture was heated under reflux for 10 hours and then evaporated to dryness. The residue was distributed between chloroform and water and the chloroform layer was separated, washed twice with water and then with saturated aqueous sodium chloride solution, dried over sodium sulphate and evaporated to dryness. The residue was dissolved in a mixture of chloroform and ethyl acetate (98:2 v/v) and the solution was loaded onto a silica gel column (Merck Kieselgel ⁶⁰/9385, 35x4cms) and eluted with chloroform/ethyl acetate (98:2 v/v). The appropriate fractions were combined and evaporated to dryness and there was thus obtained N¹-Fmoc-N²-benzyl-N²-Boc-hydrazine as a white crystalline solid (16.5g), the structure of which was confirmed by FAB mass spectroscopy (MH⁺ == 445).

A 5.2 molar solution of hydrogen chloride in ethyl acetate (50ml) was added to a solution of the above hydrazide (16.4g) in ethyl acetate (50ml). and the mixture was kept at laboratory temperature for 1 hour and then evaporated to dryness. The residue was dissolved in ethyl acetate (60ml) whereupon a gelatinous solid slowly precipitated. The solid was collected by filtration, washed with ethyl acetate followed by diethyl ether and dried and there was thus obtained N¹-Fmoc-N²-benzylhydrazine hydrochloride (9.57g), the structure of which was confirmed by FAB mass spectroscopy (MH⁺ = 345).

Triethylamine (1.4ml) and bis-succinimido carbonate (BSC, 2.56g) were added to a stirred suspension of the above hydrazide hydrochloride (3.81g) in acetonitrile (100ml) and stirring was continued at laboratory temperature. Further quantities of BSC (1.2g and 1.0g) were

- 11 -

added at 1 hour intervals. The solution was evaporated to dryness and the residue was dissolved in a small volume of a mixture of ethyl acetate and petroleum ether (bp 60-80°C) (45:55 v/v). The solution was loaded onto a silica gel column (Merck Kieselgel ⁶⁰/9385, 30x3cms) and eluted with the same ethyl acetate/petroleum ether mixture. The appropriate fractions were pooled and evaporated to dryness and there was thus obtained Fmoc-Azphe-OSu as a solidified gum (3.8g), the structure of which was confirmed by FAB mass spectroscopy (MH^+ =).

Example 4

Synthesis of N¹-Fluoren-9-ylmethoxycarbonyl-N²-methyl-N²-benzotriazol-1-yloxycarbonylhydrazine (Fmoc-Azala-OBt)

Bis-benzotriazol-1-yl carbonate (4.23g) was added to a stirred suspension of N¹-Fmoc-N¹-methylhydrazine hydrochloride (3.05g) and triethylamine (1.4ml) in acetonitrile (50ml) whereupon the suspension rapidly cleared. The mixture was stirred for 2.5 hours at laboratory temperature and then filtered. The solid residue was washed with acetonitrile and then diethyl ether, and then dried. There was thus obtained Fmoc-Azala-OBt as an amorphous solid (1.56g).

Example 5

Synthesis of N¹-Fluoren-9-ylmethoxycarbonyl-N²-benzyl-N²-benzotriazol-1-yloxycarbonylhydrazine (Fmoc-Azphe-OBt)

Bis-benzotriazol-1-yl carbonate (4.23g) was added to a stirred suspension of triethylamine (1.40ml) and N¹-Fmoc-N²-benzylhydrazine hydrochloride (3.81g) in acetonitrile (50ml) and the mixture was stirred for 3 hours at laboratory temperature and then evaporated to dryness. The residue was dissolved in a 1:2 v/v mixture of ethyl acetate and petroleum ether (bp 60-80°C.) and loaded onto a silica gel column (Merck Kieselgel ⁶⁰/9385, 35x3cms) and eluted with the same ethyl acetate/petroleum ether mixture. The appropriate fractions were pooled and evaporated to dryness and there was thus obtained Fmoc-Azphe-OBt as

- 12 -

a white foam (2.6g), the structure of which was confirmed by FAB mass spectroscopy ($MH^+ = 506$).

PP 9/157

13JUN91

RPS/JLB



THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)